Consommation et Corporations Canada
Consumer and Corporate Affairs Canada

Bureau des brevets
Patent Office

Ottawa, Canada
K1A 0C9

(11) (C) **1,283,607**

(21) 531,200

(22) 1987/03/05

(45) 1991/04/30

(52) 167-277

(51) INTL.CL.[5] A61K-31/135

(19)(CA) **CANADIAN PATENT** (12)

(54) Stable Injectable Pharmaceutical Formulation for 1,4-Dihydroxy-5-8-Bis[2-(2-Hydroxyethylamino)-Ethylamino] Anthraquinone, Dihydrochloride

(72) Niphadkar, Pradeep V. , U.S.A.
Desai, Narendra R. , U.S.A.
Jones, Paul N. , U.S.A.
Mooney, Kieran G. , U.S.A.

(73) American Cyanamid Company , U.S.A.

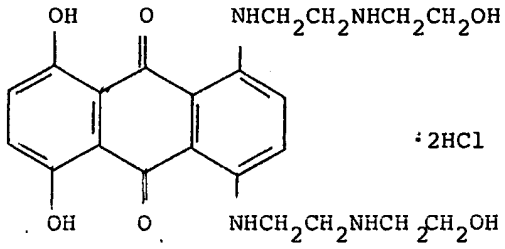
(30) (US) U.S.A. 06/837,243 1986/03/07

(57) 2 Claims

NO DRAWING

ABSTRACT OF THE DISCLOSURE

This disclosure describes stable injectable pharmaceutical formulations of NOVANTRONE®. This compound has the formula

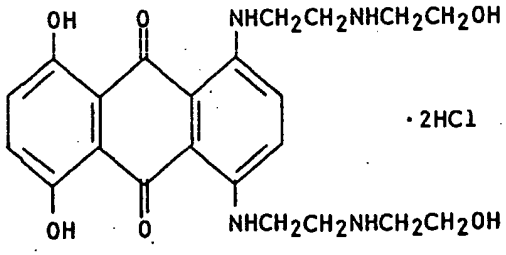


and is known as 1,4-dihydroxy-5,8-bis[2-(2-hydroxyethylamino)-ethylamino]anthraquinone.

Title: STABLE INJECTABLE PHARMACEUTICAL FORMULATION FOR 1,4-DIHYDROXY-5,8-BIS[2-(2-HYDROXYETHYLAMINO)-ETHYLAMINO]ANTHRAQUINONE, DIHYDROCHLORIDE

DESCRIPTION OF THE INVENTION

The compound 1,4-dihydroxy-5,8-bis[2-(2-hydroxyethylamino)ethylamino]anthraquinone, dihydrochloride, having the formula:



is described and claimed in U. S. Patent No. 4,197,249 and is sold under the registered trademark Novantrone® in Canada and Europe and is currently under consideration by the United States Food and Drug Administration for approval as an anti-cancer agent.

*

This compound is known to undergo oxidative degradation in aqueous solution. This degradation occurs much more rapidly in the presence of metal ions such as cuprous, cupric, ferrous, ferric, etc., even when present in minute quantities (e.g. less than 10 ppm).

Since this compound exhibits optimum pharmacological activity in humans when administered parenterally (intramuscularly, intravenously) as opposed to oral administration, it is extremely important that solutions of this compound remain stable for prolonged periods under normal storage conditions.

It has now been discovered that the inclusion of a combination of critical factors in an aqueous formulation of 1,4-dihydroxy-5,8-bis[2-(hydroxyethylamino) ethylamino]anthraquinone, dihydrochloride provides a formulation which is extremely stable under normal storage conditions.

These factors are 1) the inclusion of a suitable antioxidant, 2) specific pH range, and 3) the inclusion of a suitable metal ion chelator.

With regard to antioxidants the most effective proved to be sodium metabisulfite.

The most effective pH range was 2.0-3.5 with 3.0 being optimum.

The most effective metal ion chelator was a combination of disodium EDTA and glycine.

Since the desired injectable formulation of 1,4-dihydroxy-5,8-bis[2-(2-hydroxyethylamino)ethylamino] anthraquinone, dihydrochloride contains 1 to 5 mg of this compound per ml of formulation, this new stable formula would have a pH of 2.0 to 3.5, with 3.0 being optimal, a sodium metabisulfite concentration of 0.01 to 0.10%, with 0.05% being optimal, disodium EDTA at a concentration of 0.01 to 0.11% with 0.10% being optimal, and glycine concentration of 0.05 to 0.2% with 0.1% being optimal.

In order to prove the enhanced stability of this new formulation, formulae of the following composition were prepared and stability studies conducted.

Formula I

1,4-Dihydroxy-5,8-bis[2-(2-hydroxy-ethylamino)ethylamino]anthraquinone, dihydrochloride	2 mg/ml
Water for Injection U.S.P.	100%
Headspace	Air

Formula II

1,4-Dihydroxy-5,8-bis[2-(2-hydroxy-ethylamino)ethylamino]anthraquinone, dihydrochloride	2 mg/ml
Cupric ions	7 ppm
Water for Injection U.S.P.	100%
Headspace	Air
pH	5.50

Formula III

1,4-Dihydroxy-5,8-bis[2-(2-hydroxyethylamino)ethylamino]anthraquinone, dihydrochloride	2 mg/ml
Sodium metabisulfite	0.01%
Sodium acetate	0.005%
Acetic acid, glacial	0.046%
Sodium chloride	0.80%
Water for Injection U.S.P.	100%
pH	3.5
Headspace	Nitrogen

Formula IV

1,4-Dihydroxy-5,8-bis[2-(2-hydroxyethylamino)ethylamino]anthraquinone, dihydrochloride	2 mg/ml
Sodium metabisulfite	0.05%
Disodium EDTA	0.10%
Glycine	0.10%
Sodium chloride (Isotonic Agent)	0.786%
Water for Injection U.S.P.	100%
pH	3.0
Headspace	as indicated*

*One portion filled under nitrogen, two portions filled under air.

The results of these stability studies are given below:

Formula	Vial Size	Headspace	Temp.°C	% of Initial Potency					
				1 Day	2 Weeks	3 Weeks	4 Weeks	6 Weeks	8 Weeks
I	10 ml	Air	56		88	84.5		72	
II	10 ml	Air	56	13					
III	10 ml	Nitrogen	56				90		85
III	2 ml	Nitrogen	42				96		93
III	2 ml	Nitrogen	56				85		72
IV	10 ml	Nitrogen	56				99		
IV	2 ml	Nitrogen	42				98.6		97.9
IV	10 ml	Air	56				98		97.6
IV	10 ml	Air	42				98		97.5
V	10 ml	Nitrogen	56				99		98.4

The above results show the superiority of the new formulation of this invention over the previous formulation and an aqueous solution of this drug.

Like most other anticancer drugs, the dose of Novantrone® is based upon the patient's body surface area and disease state. It is highly advantageous from cost and marketing point of views to have Novantrone® product available in small size containers like 2 ml vials. However, because of relatively higher headspace to volume ratio of smaller vials as against the larger vials, the stability of this product becomes critical in small 2 ml vials. It is important to note that the new formulation was found to be superior to the previous formulation in both small as well as relatively larger volume vials.

To further illustrate the stability of this invention a composition was prepared as follows.

Formula V

1,4-Dihydroxy-5,8-bis[2-(2-hydroxy-ethylamino)ethylamino]anthraquinone, dihydrochloride	2 mg/ml
Disodium EDTA	0.10%
Sodium metabisulfite	0.04%
Glycine	0.10%
Sodium chloride (Isotonic Agent)	0.60%
Water for Injection U.S.P.	100%
pH	3.0

This formula (V) and a composition of formula (I) each had cupric ions added to a concentration of 6 ppm and were then placed in a stability study at 56°C for 4 weeks. The results at the end of this time showed that formula (I) lost 98% of its potency in 2 days while formula (V) retained 98.6% potency after 4 weeks.

CLAIMS

We claim:

1. A pharmaceutical formulation comprising from 1 to 5 mg per ml of formulation of 1,4-dihydroxy--5,8-bis[2-(2-hydroxyethylamino)ethylamino]anthraquinone, dihydrochloride in an isotonic solution at a pH of from 2.0 to 3.5, containing sodium metabisulfite at a concentration of from 0.01 to 0.10%, disodium EDTA at a concentration of from 0.01 to 0.11% and glycine at a concentration of from 0.05 to 0.20%.

2. A formulation according to Claim 1 where the concentration of 1,4-dihydroxy-5,8-bis[2-(2-hydroxyethylamino)ethylamino]anthraquinone, dihydrochloride is 2 mg/ml and the concentrations of sodium metabisulfite, disodium EDTA and glycine are 0.05%, 0.10% and 0.10% respectively.

SMART & BIGGAR
OTTAWA, CANADA

PATENT AGENTS

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente